BIOLOGY OF DEVELOPMENT AND AGING (BDA) GUIDELINES

The Biology of Development and Aging Integrated Review Group (IRG) will consider research applications that are focused on Development and/or Aging and that employ approaches at a variety of levels from molecules to whole organisms. Development and Aging are inherently integrative research areas focusing on biological changes over time. Proposals in this IRG will frequently transcend the boundaries of single organs or systems.

Areas of review related to development include:

Morphogenesis and pattern formation; gastrulation; cell fate, lineage and differentiation; organogenesis; gametogenesis; pre- and post-implantation development; regeneration; evolutionary aspects of development; and the molecular basis of primordial birth defects.

Areas of review related to both development and aging include:

Chromosome dynamics; cell cycle control; cell death; responses to stress; cellular signaling; the biology and applications of stem cells; and tissue repair.

Areas of review related to aging include:

Determinants of longevity; age-related changes in physiological functions; geriatric syndromes and diseases; animal models of aging; predictive markers of biological health and aging; and mechanisms of exceptional aging.

The following study sections are included in this IRG:

Development 1 (DEV-1)
Development 2 (DEV-2)
Cellular Mechanisms in Aging and Development (CMAD)
Aging Systems and Geriatrics (ASG)

The study sections of the Biology of Development and Aging IRG are among the first of the new or reorganized study sections to be proposed for implementation. As a result, some of the Teams that will develop recommendations for other IRGs that may share interests in areas of research with the BDA IRG have not yet met or completed their deliberations. Therefore, the proposed “shared interest” guidelines for each of the study sections listed below are tentative, pending further input from the remaining study section design Teams, the scientific community, and the CSR Advisory Committee to the Director, CSR.

The expectation is that each of these study sections will receive 50 or more applications. However, in the event of fewer applications, adjustments may be necessary, e.g., as near mirror image study sections, DEV-1 and DEV-2 could be combined.

Development -1 Study Section (DEV-1)

This study section reviews applications covering a wide range of topics in developmental biology using diverse animal and plant models. Cellular, biochemical, genetic and

molecular approaches to developmental problems at the level of cells, tissues, organs and the whole organism are appropriate. Emphasis is on the development of the gametes and on organogenesis.

- Gametogenesis in studies having a developmental focus: Includes imprinting, meiosis, germ cell/somatic cell interactions, and the processes leading to the formation of eggs and sperm.

- Pre-implantation, implantation and placental development in studies aimed elucidation of general developmental mechanisms.

- Animal cloning: Includes techniques of embryo splitting as well as introduction of donor nuclei into host eggs.

- Organogenesis: Includes signaling and morphogenetic pathways that lead to initial establishment of organ primordia, such as gonads, reproductive tract, heart, lung, limbs, brain and spinal cord, and endodermal organs.

- Differentiation: Includes changes in gene expression and all processes leading to tissue formation and the adoption of specific cell fates.

- Signaling in development: Includes intercellular signals and activation of receptor-mediated signaling pathways leading to changes in developmental potential or fate or differentiation, particularly in the context of the development of the gonads and gametes and in organogenesis.

- Regulatory networks: Include whole genome approaches to profile and analyze regulatory networks in development, particularly in the context of the development of the gonads and gametes and in organogenesis.

- Regeneration: includes regeneration following amputation or injury of organs, limbs, and the nervous system when the focus is a basic developmental question.

- Metamorphosis: Includes both invertebrate and vertebrate metamorphosis.

- Apoptosis: Focuses on how this process participates in developmental processes rather than general apoptotic mechanisms.

<u>DEV-1: Areas of Shared Interest</u>
Within IRG:
DEV-1 overlaps substantially with the Development-2 (DEV-2) study section with the exception that organogenesis and gametogenesis are emphasized in DEV-1.

Outside IRG:
IRG 2 Molecular Approaches to Gene Function
IRG 3 Molecular Approaches to Cell Function and Interactions
IRG 4 Fundamental Genetics & Population Biology
Cell biological and genetic studies, when those studies emphasize a developmental question, could be reviewed in DEV-1 as opposed to study sections in IRGs 2, 3, & 4.

IRG 10 Immunology
IRG 13 Oncology
IRG 14 Hematology
IMM, ONC, and HEM have developmental components. When the focus of an immunology, oncology, or hematology application is late development, assignment could be to IRGs 10, 13, or 14. When the focus is basic, early development, assignment could be to DEV-1 or -2. Areas of shared interest may include stem cells, apoptosis, and cell cycle control.

IRG 16 Endocrine, Metabolism, Nutrition & Reproductive Sciences (EMNR)
Shared interest exists between EMNR and BDA in the areas of meiosis and animal cloning as well as in gonadal and endocrine organogenesis. In general, applications on meiosis and animal cloning that focus on reproductive competency or success would be assigned to the EMNR IRG. Similarly, applications that focus on development (such as cell cycle control, apoptosis, cell fate, or early pattern formation) would be assigned to DEV-1 or -2. In general, when the question being addressed is germane to the development of more than a single organ system, either because it addresses the "primordial organ" or because of the generality of the process being studied, the application would be assigned to BDA. Developmental studies focused on development of a specific organ should be reviewed in the context of that organ system (EMNR in the case of endocrine glands and reproductive organs). The overall philosophy is that assignment should be made based on the central focus of the application.

IRG 15 Cardiovascular Sciences
IRG 17 Musculoskeletal, Oral and Skin Sciences
IRG 18 Digestive Sciences
IRG 19 Pulmonary Sciences
IRG 20 Renal & Urological Sciences
DEV-1 and -2 include basic, early developmental mechanisms involved in formation of organ primordia, such as muscle, skeleton, skin, liver, lung, and kidney. Studies involving maturation of organ physiology or the physiology and function of developed organs could be assigned to other IRGs such as 15 and 17-20. Overlapping interests may include stem cells, apoptosis, and regulation of cell cycle.

IRG 22 Molecular, Cellular, & Developmental Neuroscience (MDCN)
Studies involving maturation of brain and spinal cord or their physiology and function as developed organs may be assigned to IRG 22, MDCN. DEV-1 may include basic, early developmental mechanisms involved in formation of organ primordia, such as the nervous system.

Development-2 Study Section (DEV-2)

This study section reviews applications covering a wide range of topics in developmental biology using diverse animal and plant models. Cellular, biochemical, genetic and molecular approaches to developmental problems at the level of cells, tissues, organs and the whole organism are appropriate. Emphasis is on pattern formation, stem cells, evolution, primordial birth defects, and early embryonic development.

- Pattern formation: Includes the process of cells establishing and refining boundaries that lead to morphological and biochemical patterns.

- Signaling in development: Includes intercellular signals and activation of receptor-mediated signaling pathways leading to changes in developmental potential or fate or differentiation.

- Regulatory networks: Include whole genome approaches to profile and analyze regulatory networks in development, particularly in the context of pattern formation, primordial birth defects, and early embryonic development.

- Induction: Includes cell-cell interactions leading to one or both cell types adopting a new cell fate.

- Cell polarity: Includes the establishment and maintenance of cell polarity in eggs and embryos including localization of determinants, localization of signaling molecules, and localization and functions of structural proteins that participate in this process.

- Cell lineage: Includes the spatial and temporal monitoring of a cell and its progeny cells during all of development.

- Apoptosis: Focuses on how this process participates in developmental processes rather than general apoptotic mechanisms.

- Evolution of development: Includes comparative development to understand conserved developmental processes and how they evolved.

- Gastrulation: Includes all aspects of how germ layers of an embryo are formed in terms of cell biology, cell movements, and signaling processes.

- Morphogenesis: Includes cell and tissue movements leading to the development of form.

- Epithelial-mesenchymal transition: Includes cell fate changes in embryos and in organ formation between epithelial and mesenchymal tissues.

- Cell migration: Includes the dynamic cell mixing and behavior inherent in all aspects of development, including gastrulation and nervous system development.

- Birth defects: Includes mechanism-based analyses of primordial birth defects.

- Stem cells: Includes stem cell biology with regard to totipotency and cell commitment.

<u>DEV-2: Areas of Shared Interest</u>
Within IRG:
The DEV-2 study section overlaps substantially with DEV-1 with the exception that pattern formation, early development, and birth defect syndromes are emphasized in

DEV-2. Applications focusing on stem cell biology with regard to totipotency and cell commitment could be assigned to DEV-2. Applications on stem cells that would be appropriate for CMAD would include studies of stem cells in relation to aging and tissue repair. The DEV-2 study section overlaps with CMAD in the areas of apoptosis and signaling.

Outside IRG:
IRG 2 Molecular Approaches to Gene Function
IRG 3 Molecular Approaches to Cell Function and Interactions
IRG 4 Fundamental Genetics & Population Biology
Cell biological and genetic studies may be assigned to DEV-2 when those studies emphasize a developmental question. If the focus is cell biological or genetic, then assignment to IRGs 2-4 may be appropriate.

IRG 10 Immunology
IRG 13 Oncology
IRG 14 Hematology
IMM, ONC, and HEM have developmental components. When the focus of an immunology, oncology, or hematology application is late development, assignment could be to IRGs 10, 13, or 14. When the focus is basic, early development, assignment could be to DEV-1 or -2. Areas of shared interest may include stem cells, apoptosis, and cell cycle control.

IRG 16 Endocrine, Metabolism, Nutrition & Reproductive Sciences (EMNR)
Shared interest exists between EMNR and BDA in the areas of meiosis and animal cloning as well as in gonadal and endocrine organogenesis. In general, applications on meiosis and animal cloning that focus on reproductive competency or success would be assigned to the EMNR IRG. Similarly, applications that focus on development (such as cell cycle control, apoptosis, cell fate, or early pattern formation) would be assigned to DEV-1 or -2. In general, when the question being addressed is germane to the development of more than a single organ system, either because it addresses the "primordial organ" or because of the generality of the process being studied, the application would be assigned to BDA. Developmental studies focused on development of a specific organ should be reviewed in the context of that organ system (EMNR in the case of endocrine glands and reproductive organs). The overall philosophy is that assignment should be made based on the central focus of the application.

IRG 15 Cardiovascular Sciences
IRG 17 Musculoskeletal, Oral and Skin Sciences
IRG 18 Digestive Sciences
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DEV-1 and -2 include basic, early developmental mechanisms involved in formation of organ primordia, such as muscle, skeleton, skin, liver, lung, and kidney. Studies involving maturation of organ physiology or the physiology and function of developed organs could be assigned to other IRGs such as 15 and 17-20. Overlapping interests may include stem cells, apoptosis, and regulation of cell cycle.

IRG 22 Molecular, Cellular, & Developmental Neuroscience

DEV-2 includes basic developmental mechanisms involved in formation of organ primordia such as brain and spinal cord. Applications focused on developmental neuroscience may be assigned to IRG 22.

Cellular Mechanisms in Aging and Development Study Section (CMAD)

CMAD reviews applications involving molecular and cell biological mechanisms of development and aging, encompassing studies ranging from single cells to whole organisms. The focus is on temporal aspects of: chromosome dynamics, cell death, cell-cycle control, cellular responses to stress, cellular communication, stem cells, physiologic regulation, and determinants of longevity and other age-related functional changes.

Specific areas covered by CMAD:

- Aspects of chromosome dynamics relevant to development and aging, including: telomeres; helicases; DNA damage and repair; and chromosome stability.

- Cell death, apoptotic and necrotic, especially as related to development and aging, including age-related degenerative diseases.

- Molecular mechanisms of age-related changes at the cellular or tissue level, e.g., endocrine/reproductive, musculoskeletal, cardiovascular, and immunological.

- Cell cycle control, including the control of embryonic cell cycles and replicative senescence.

- Cellular responses to stress, including embryonic, fetal and adult responses such as: oxidative damage; mitochondrial dysfunction; transcriptional, translational and post-translational modifications and chemical modifications of other cellular components.

- Aspects of cellular communication especially as related to aging, including: intracellular, intercellular, and matrix-cell communication; signaling pathways; gene regulation; and cell differentiation.

- Fundamental biology of stem cells, including: their application to development and disease; their role and use in tissue regeneration and repair; stem cell senescence and death.

- Genetic and environmental determinants of longevity and age-related functional changes, including: fetal origins of adult disease; mechanistic aspects of metabolic imprinting; dietary restriction; and mechanistic aspects of genetic and hormonal manipulation of organismal longevity.

- Evolution of aging, including comparative studies of mechanisms of aging.

CMAD: Areas of Shared Interest
Within IRG:

Areas of overlap between CMAD and DEV-1/DEV-2 include studies of stem cells and apoptosis. Distinguishing features of applications appropriate for CMAD would include studies of stem cells in relation to aging and tissue repair, basic cellular and molecular properties of stem cells and apoptosis, apoptosis in degenerative diseases, and cellular signaling as related to mechanisms of aging.

Proposals that concern areas of overlap between CMAD and ASG, such as those dealing with approaches to enhancing longevity, would be more appropriately assigned to ASG if they focus on organ or multi-organ physiology as opposed to cellular or molecular mechanism.

Outside IRG:
CMAD appropriately reviews fundamental mechanistic studies that relate to both developmental disorders and the pathobiology underlying aging and degeneration. Studies designed to address general principles, particularly those not focused on a developmental or aging process, may be considered by the appropriate organ-focused IRG.

IRG 1 Biochemical chemistry and Macromolecular Biophysics
Studies designed to address principles of chemistry and biophysics, unrelated to organism development, aging and their perturbations could be appropriately considered by IRG 1. Studies using the general principles of chemistry and biophysics to address development, aging, and their perturbations could be appropriately considered by CMAD.

IRG 2 Molecular Approaches to Gene Function
IRG 3 Molecular Approaches to Cell and Molecular Function
Studies designed to address the general principles of gene and cell function, unrelated to whole organism development, aging and their perturbations could be appropriately considered by IRG 2 and 3. Studies using the general principles of gene and cell function to address development, aging, and their perturbations could be appropriately considered by CMAD.

IRG 4 Fundamental Genetics and Population Biology
Studies designed to address basic genetic principles in humans and model organisms, unrelated to whole organism development, aging, and their perturbations could be appropriately considered by IRG 4. Studies using genetic principles to address development, aging, and their perturbations could be appropriately considered by CMAD.

IRG 13 Oncological Sciences
Studies of genetic instability related to cancer diagnosis, prognosis, and treatment could be appropriately assigned to IRG 13. Studies of cancer in the context of development or aging, particularly in multiple organs, could be assigned to CMAD.

IRG 14 Hematology
IRG 15 Cardiovascular Sciences
CMAD may review fundamental mechanistic studies that relate to both developmental disorders and the pathobiology underlying aging and degeneration, particularly when the studies transcend single organ systems or disciplines. Studies designed to address mechanistic principles, not focused on a developmental or aging process, may be

considered by the appropriate organ-focused IRG such as IRG 14 or 15. Overlapping interest may include arterial sclerosis associated with aging.

IRG 16 Endocrinology, Metabolism, Nutrition and Reproductive Sciences (EMNR)
Studies of hormonal and nutrient manipulations to increase the lifespan may be appropriately assigned to CMAD or ASG. If the focus is a better understanding of diabetes, nutrition, or hormone action per se, assignment could be to EMNR. Shared interests may include cell cycle control and apoptosis.

IRG 17 Musculoskeletal, Oral and Skin Sciences
IRG 18 Digestive Sciences
IRG 19 Pulmonary Sciences
IRG 20 Renal & Urological Sciences
CMAD may review fundamental mechanistic studies that relate to both developmental disorders and the pathobiology underlying aging and degeneration, particularly when the study transcends single organ systems or disciplines. Studies designed to address mechanistic principles, particularly those not focused on a developmental or aging process may be considered by the appropriate organ-focused IRG such as IRGs 17- 20. Areas of shared interest may include degeneration/regeneration and pharmacological changes with aging.

Aging Systems and Geriatrics Study Section (ASG)

The Aging Systems and Geriatrics study section reviews applications involving aging humans or animals, in particular studies of postmaturational changes, which transcend single organ systems or disciplines, and which may require integrated experimental, genetic or observational approaches.

Specific Areas covered by Aging Systems and Geriatrics:

- Age-related changes in the regulation of complex physiological functions, such as the musculoskeletal system (including motor function, postural control, and balance); metabolic/endocrine systems (including impaired glucose tolerance); reproductive systems (including menopause and andropause); host defense responses to infection, injury or other stresses (including immunologic function); blood pressure; body weight, body temperature, fluid and electrolyte homeostasis, as well as the study of interventions to ameliorate these age-related changes.

- Geriatric syndromes (i.e., age-related conditions involving multiple systems and/or multifactorial mechanisms) and their prevention or treatment. These include: falls, syncope, frailty, immobility, delirium, incontinence, polypharmacy, malnutrition, mood disorders, sarcopenia, chronic pain, loss of functional independence, and failure to thrive. Interventions may include exercise, hormones, nutrition, medications, technology, and lifestyle modifications.

- Descriptive, mechanistic, and intervention studies of geriatric diseases affecting multiple body systems that are unique or highly prevalent in elderly people or aging animals. The focus should be on an aging population, the role of comorbid health conditions, or complex outcomes relating to overall functional status and multiple systems. Examples include congestive heart failure (especially, diastolic

dysfunction), atrial fibrillation, hypertension (especially systolic hypertension), type 2 diabetes and its complications, osteoarthritis, osteoporosis and related bone fractures.

- Regulation of life span and rates of aging changes in animal models employing approaches such as comparative biology, caloric restriction, and animals especially resistant to aging processes.

- Development and validation of predictive markers of biological health and aging.

- Studies of mechanisms of exceptional aging, including premature aging syndromes, extreme longevity and factors contributing to sustained health without significant diseases or disability into advanced age.

- Age-related changes in pharmacokinetics and dynamics.

- Modeling of complex regulatory networks (such as those affecting cardiovascular function, circadian rhythms, and postural control) and their alteration with age.

<u>ASG: Areas of Shared Interest</u>
Within IRG:
Studies with a primary focus on physiologic mechanisms of aging, geriatric syndromes and the effect of aging on manifestations of geriatric diseases and/or involving multiple organs or systems could be reviewed by ASG. Studies focused on basic molecular and cellular aspects of aging could be reviewed by CMAD when those studies concern fundamental cell or molecular biology and by ASG when those studies concern systems-level approaches or analyses.

Outside IRG:
IRG 6 Bioengineering Sciences & Technologies
Applications that focus on basic modeling techniques could be assigned to IRG 6. Applications that apply modeling techniques to the aging process could be assigned to ASG.

IRG 7 Health of the Population
IRG 8 Risk Prevention & Health Behavior
IRG 9 Behavioral and Biobehavioral Processes
Applications with a primary focus on physiologic or biological processes could be reviewed by ASG when an aging population is specifically studied. However, applications with a primary focus on behavioral or social antecedents or outcomes, e.g., epidemiologic studies, dementia, falls, mood disorders, behavioral prevention and management of physical diseases, and cognitive or linguistic impairments, could be reviewed by IRGs 7-9.

IRG 13 Oncological Sciences
IRG 14 Hematology
IRG 15 Cardiovascular Sciences
Studies primarily focused on a single organ or system or a specific disease in which age-related interactions or changes of function are a minor or secondary component could be reviewed by the appropriate organ or system IRG, such as IRGs 13-15. Studies in which

the focus is aging, particularly those that transcend single organ systems or disciplines, could be reviewed in ASG. Cancer and arterial sclerosis, though increased in prevalence with age, could remain with IRG 13 or 15, except when the focus is on the contribution of the aging process rather than on the disease.

IRG 16 Endocrine, Metabolism, Nutrition & Reproductive Sciences (EMNR)
Male and female reproductive aging across and within the hypothalamic-pituitary-gonadal (H-P-G) axis and other reproductive tissues where the focus is on the endocrine system could be assigned to EMNR. If the focus is on mechanisms of aging, such as oxidative stress, DNA damage, or cellular senescence, particularly when the study transcends single organ systems or disciplines, the applications could be assigned to ASG. Interactions between the H-P-G axis and non-reproductive physiologic systems could be assigned to ASG if the focus is on aging research. Areas of unavoidable shared interest such as menopause would be resolved according to the central focus of the application.

IRG 17 Musculoskeletal, Oral and Skin Sciences
Aging studies that use the musculoskeletal system as a model to address questions having applicability beyond the musculoskeletal system may be assigned to ASG. Studies that address questions applicable to the musculoskeletal system or its diseases may be assigned to IRG 17. When osteoporosis is a secondary aspect of a multi-system study of the aging process, assignment could be to ASG; when osteoporosis is the primary focus of study, assignment could be to IRG 17. Studies of aging, disability, and rehabilitation medicine are shared with IRG 17. Musculoskeletal studies involving interactions with age-related changes in other physiological systems could be assigned to ASG. When musculoskeletal function or rehabilitation is the primary study focus, assignment could be to IRG 17.

IRG 18 Digestive Sciences
IRG 19 Pulmonary Sciences
IRG 20 Renal & Urological Sciences
Studies primarily focused on a single organ or system or a specific disease in which age-related interactions or changes of function are a minor or secondary component could be reviewed by the appropriate organ or system IRG, such as IRGs 18-20. Studies in which the focus is aging, particularly those that transcend single organ systems or disciplines, could be reviewed in ASG. Areas of shared interest may include pharmacokinetic changes during aging.

IRG 23 Integrative, Functional, & Cognitive Neuroscience (IFCN)
Applications with a primary focus on aging aspects of motor movement integration or memory could be reviewed by ASG particularly when the studies transcend single organ systems or disciplines. Aging studies of motor movement integration and memory in the context of cognitive neuroscience could be assigned to IRG 23.

IRG 24 Brain Disorders & Clinical Neuroscience (BDCN)
Applications with a primary focus on specific neurological diseases, such as Alzheimer's disease, could be reviewed in IRG 24; however, proposals focused on multiple system manifestations of such diseases, including gait abnormalities, could be reviewed by ASG.